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ASSOCIATE VICE PRESIDENT
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PhRMA

00 OCT October 31, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 00D-1335 - FDA Draft Guidance for Industry on Allergic Rhinitis: Clinical Development Programs for Drug Products (65 Federal Register 38563; June 21, 2000)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is submitting this set of comments on the above "Draft Guidance for Industry." PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. PhRMA member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invest over $26 billion annually in the discovery and development of new medicines.

The following comments have been organized by 'Section' and 'Line Number' as requested in the guidance document.

III. OVERALL CONSIDERATIONS - ADULT PROGRAM

A.1. Number of Trials

Line 58: This guidance allows for the submission of one PAR and one SAR Phase 3 trial in support of both indications for a new NDA based on the premise that these are related disorders. However, if a Sponsor has an approved NDA for one of the two related disorders of allergic rhinitis, e.g., SAR, in order to get the other indication, i.e., PAR, it is unclear if the FDA will still require two adequate and well-controlled clinical trials for the new indication. Clarification is requested.

A.2 Dose

Lines 70-71: Additional guidance regarding the most appropriate study design for dose-ranging studies in allergic rhinitis would be helpful. We assume from the guidance that the dose-ranging study can be conducted either in SAR or PAR patients to establish the dose for both indications.

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A.3. Safety Monitoring

Line 106: Regarding assessment of sedation, the guidance mentions some assessment of degree of sedation compared to placebo should be provided in the safety database. However, the FDA should provide general criteria for classifying a product as sedating, non-sedating, or mildly sedating. PhRMA believes that the assessment of sedation should be broadened to include not only AE reports but, "*other specific measures of sedation as agreed between the Sponsor and FDA*".

A.4. Corticosteroid Issues

Line 127: The reference to inclusion of oral prednisone as a positive control should be deleted; there is no need to subject patients to this treatment for this purpose. Other PK/PD models for assessing the HPA axis effects of intranasal corticosteroids are available.

Line 130: The slit lamp examinations and intra-ocular pressure testing for cataracts and glaucoma should be included in protocols for long term clinical studies only.

IV. OVERALL CONSIDERATIONS – PEDIATRIC PROGRAM

A. New Molecular Entity or New Pediatric Indication

Line 243: PhRMA agrees that Sponsors should discuss the specifics of any pediatric program with the Division. However, since the earliest clinical manifestation of allergic rhinitis is 2-years of age, we suggest that the guidance should be changed to only require testing of drugs indicated for allergic rhinitis down to the age of 2-years rather than 6-months.

Line 245: PhRMA suggests that the two adequate and well controlled studies in children may be conducted in different age groups.

A.2. Drugs Already Studied in Adults

Line 269: PhRMA requests that FDA include specific parameters to clarify the statement, "*adequate short and long-term safety information for the proposed pediatric age group".*

A.3. Safety Data

Line 281: PhRMA interprets the long-term safety requirements for the pediatric program to be three additional months of specific pediatric safety data for intranasal products and one additional month of safety data for oral products from placebo-controlled trials. If this is not a correct interpretation, clarification is requested.

A.4. Corticosteroid Issues

Line 297: It would be helpful for the Agency to develop published guidance about stadiometry studies.

V. PROTOCOL ISSUES AND ELEMENTS

A. Trial Design

Line 347: PhRMA recommends adding "excluding patients who have a pre-determined drop in symptom scores during their placebo run-in period." It is usually impractical to include a vehicle placebo run-in period in a SAR study.

Line 358: With respect to pollen counts, we believe that extensive pollen counts will provide limited value as the placebo-control and randomization already control for this variability. Additionally, it is unlikely that the extent of patient exposure to outdoor air or number of rain days can be reliably documented or be used to generate meaningful data for large multicenter studies.

Line 368: The desire to restrict the conduct of PAR studies to periods when SAR allergens are less abundant is commendable; however, this will not be practical for studies intended to collect long term safety data. The guidance should be clarified to indicate that this comment refers to 4 week efficacy data only.

B. Inclusion Criteria

Line 380: We recommend that the FDA consider modifying the definition of a positive skin test as a wheal $\geq$ 5mm larger than the diluent control for intradermal testing to conform to common medical practice, rather than $\geq$ 7mm which is stated in the guidance.

Line 390: We recommend that patients should not start immunotherapy for 3-months preceding enrollment, rather than the one-month timeframe stated in the guidance.

C. Exclusion Criteria

Line 421: A washout period of 5 days for fexofenadine should be added.

F.3. Rating System

Line 479: We feel that the reflective scoring system, as it is well validated, should be the method of choice. We do not believe that instantaneous scoring is necessary, since the pre-specified time interval in the reflective score should include information on the degree of effectiveness immediately prior to the next dose.

Line 482: Addition or deletion of symptoms to/from the composite or total score should be discussed with the Division on a case by case basis. Nasal congestion should not automatically be excluded from a composite or total nasal symptom score for antihistamines.

VI. DATA ANALYSIS ISSUES

D. Onset of Action

Line 582: The requirement for maintenance/consistency of a statistically significant difference, which should also be a clinically relevant difference, should be further defined.

Line 588: It states that the onset of action trials do not have to be done in both SAR and PAR. Therefore, it is inferred that the onset of action claims will be applicable to both indications, if they were conducted in only PAR or SAR given the similarities in these disorders? Clarification is requested.

VII. SAR PROPHYLAXIS TRIALS

Line 635: It is discussed that a prophylaxis claim should be based on a standard allergic rhinitis trial and not an EEU trial. We interpret this to mean that if a Sponsor conducted one standard allergic rhinitis trial, as opposed to an EEU trial, this would support an SAR prophylaxis claim? Clarification is requested.

PhRMA trusts that these comments are useful to the FDA, as this Guidance is finalized.

Sincerely,